

Seizure anticipation techniques: state of the art and future requirements

K. Lehnertz

Department of Epileptology, Bonn University Medical Center
Sigmund Freud Str 25, 53105 Bonn, Germany

Abstract- Recent research in seizure anticipation has shown that "pre-seizure states" can be detected several minutes in advance from analysis of EEG time series. This time frame would allow development and testing of specific seizure prevention techniques. Thus, there is now growing interest to bring these analysis techniques to a broader application in hospitals. Similar demands come from the industry as there is strong interest to incorporate analysis techniques into EEG acquisition systems and, moreover, to develop miniaturized possibly implantable devices for seizure anticipation and possibly prevention. This report gives an overview of the state of the art of seizure anticipation techniques and addresses future requirements to allow realization of seizure anticipation devices.

Keywords - Time series analysis, EEG, epilepsy, seizure anticipation, implantable devices

I. Introduction

One of the most disabling aspects of epilepsy is that seizures appear to be unpredictable. Although there is a considerable bulk of literature the mechanisms underlying seizure generation are not yet fully explored. In EEG analysis the search for the *hidden information* predictive of an impending seizure has a long history. As early as 1975, researchers considered analysis techniques like pattern recognition analytic procedures of spectral data [1] or autoregressive modeling of EEG data [2] for predicting epileptic seizures. Findings indicated that EEG changes characteristic for pre-seizure states may be detectable, at most, a few seconds before the actual seizure onset. None of these techniques were implemented clinically. Apart from applying signal analysis techniques the relevance of steep, high amplitude epileptiform potentials (so called *spikes*, the hallmark of the epileptic brain) has been investigated in a number of clinical studies [3-5]. While some authors reported on a decrease or even total cessation of spikes before seizures, re-examination did not confirm this phenomenon in a larger sample.

In recent years, technical advantages such as digital video-EEG monitoring systems as well as an increased computational power led to a highly sophisticated clinical epilepsy monitoring allowing to process huge amounts of data in real-time. In addition, chronically implanted intracranial electrodes allow continuous recording of brain electrical activity from the surface of the brain and/or from within specific brain structures with a high signal-to-noise ratio and with a high spatial resolution.

II. State of the art of seizure anticipation techniques

Recent research in seizure anticipation has shown that evident markers in the EEG representing the transition from asynchronous to synchronous states of the epileptic brain (*pre-seizure state*) can be detected on time scales ranging from several minutes up to hours (cf. Fig. 1). With these findings it was hypothesized that the ability to anticipate epileptic seizures would dramatically change therapeutic possibilities and would eventually decrease both the risk of injury and the feeling of helplessness resulting from the unpredictable occurrence of seizures.

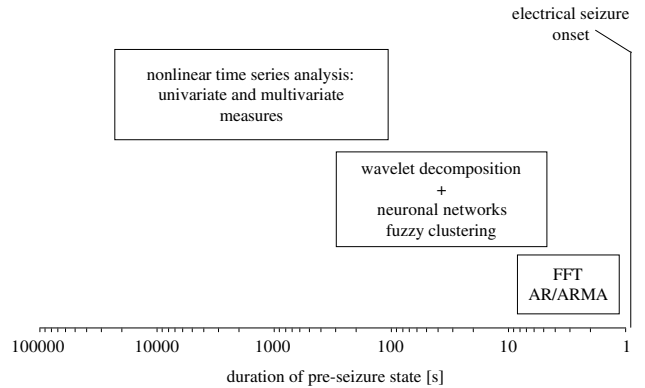


Fig. 1. Duration of pre-seizure states relative to electrical seizure onset obtained from analyses of intra- or extracranial EEG recordings using different time series analysis techniques [6-10,12-25].

Analysis techniques applied to both intra- and extracranial EEG recordings so far can be divided into two main concept-based categories: *Linear* time series analysis techniques mainly involve spectral analysis using FFT, spectral estimation based on parametric modeling (AR/ARMA models), signal wavelet decomposition, analysis of phase relationships or coherence, as well as extraction of time-domain based descriptors [6-10]. *Nonlinear* time series analysis techniques [11] mainly involve estimates of an effective correlation dimension, entropy related measures, the largest Lyapunov exponent, measures for determinism, similarity, or interdependencies, as well as recurrence quantification [12-22]. Both categories are complemented by pattern recognition techniques such as recurrent neuronal networks [23], cellular neuronal networks [24], or fuzzy clustering [25].

Usually these techniques are applied to long-lasting multi-channel recordings in a moving-window technique. Depending on the complexity of the applied analysis technique computation times vary between a few milliseconds up to some

Report Documentation Page

Report Date 25 Oct 2001	Report Type N/A	Dates Covered (from... to) -
Title and Subtitle Seizure Anticipation Techniques: State of the Art and Future Requirements		Contract Number
		Grant Number
		Program Element Number
Author(s)	Project Number	
	Task Number	
	Work Unit Number	
Performing Organization Name(s) and Address(es) Department of Epileptology, Bonn University Medical Center Sigmund Freud Str 25, 53105 Bonn, Germany		Performing Organization Report Number
Sponsoring/Monitoring Agency Name(s) and Address(es) US Army Research, Development & Standardization Group (UK) PSC 802 Box 15 FPO AE 09499-1500		Sponsor/Monitor's Acronym(s)
		Sponsor/Monitor's Report Number(s)
Distribution/Availability Statement Approved for public release, distribution unlimited		
Supplementary Notes Papers from 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Oct 25-28, 2001, held in Istanbul, Turkey. See also ADM001351 for entire conference on cd-rom		
Abstract		
Subject Terms		
Report Classification unclassified	Classification of this page unclassified	
Classification of Abstract unclassified	Limitation of Abstract UU	
Number of Pages 3		

tenth of seconds. Thus, most applications can be performed in real-time using standard personal computers.

III. Future requirements

Results obtained so far underline the high impact of both linear and nonlinear EEG analysis techniques for a timely detection of pre-seizure states. Given the technologies currently available as well as rapid technological developments, realization of implantable seizure anticipation and prevention systems can be envisaged. However, in order to achieve an unequivocal definition of a pre-seizure state from either invasive or non-invasive recordings a variety of studies have to be carried out beforehand:

(1) Up to now findings were exclusively obtained from retrospective studies in well elaborated cases (predominantly unilateral focal epilepsies). Thus, evaluation of more complicated cases as well as prospective studies on a larger population of patients including different types of epilepsies are necessary.

(2) Most studies carried out so far have concentrated on EEG recordings just prior to seizures. However, other studies [7,8,12,26,27,28] have shown that there are phases of dynamical changes even during the seizure-free interval pointing to abnormalities but are not followed by a seizure. Moreover, a variety of pathologically or physiologically induced dynamical interactions are not yet fully understood. Among others, these include different sleep stages, different cognitive states, as well as daily activities that clearly vary from patient to patient. Thus, in order to evaluate specificity of possible seizure anticipation techniques analyses of long-lasting multi-channel EEG recordings covering different pathological and physiological states is mandatory [13,19].

(3) In order to allow broader clinical applications analyses of non-invasively recorded EEG have to be carried out. Although some studies [2,10,15,18] indicate that pre-seizure states can be detected using scalp EEG recordings, specificity of these findings is hard to evaluate since again these studies lack the comparison with sub-critical state changes during the seizure free interval. A problem particularly related to analyses of scalp EEG recordings is the definition of the *unequivocal time of seizure onset*. In case of seizures originating in deep brain structures scalp EEG recordings usually pick up the spreading of seizure activity to more superficial brain areas rather than the *unequivocal EEG onset* of a seizure. Depending on the individual properties of seizure spread, only anticipation times longer than a few seconds can be assumed reliable. In contrast to analyses of invasive EEG recordings the spatio-temporal dynamics of the epileptogenic process is notoriously difficult to study through scalp EEG time series. This is mainly due to a poorer signal-to-noise ratio and because of contamination with physiological and technical artifacts that are hard to avoid during long-term EEG recordings. Thus, development of refined artifact detection and elimination techniques has to be carried out.

(4) A further problem that relates to both invasive and non-invasive EEG recording methodologies is the minimum number of sensing electrodes and the minimum distance to the epileptic focus to allow unequivocal definition of a pre-seizure state. Several recent studies indicate an improved detectability of pre-seizure states when applying multivariate time series analysis techniques [8,12,16,17,18,28]. These studies provide evidence that a minimum number of sensing electrodes and a minimum distance to the seizure generating area can be estimated.

(5) EEG analysis techniques have to be further improved to allow better characterization of non-stationarity and high-dimensionality in brain dynamics, as well as to disentangle even subtle dynamical interactions between pathological disturbances and surrounding brain tissue.

(6) Depending on the complexity of EEG analysis techniques and depending on the number of recording channels necessary to allow unequivocal detection of a pre-seizure state, the use of powerful computer systems is still required. Thus, optimization of underlying algorithms and development of a powerful and possibly miniaturized analyzing system are necessary. This system will likely require processing of multi-channel data in parallel as well as optimization for each patient. Given the potential for seizures to alter brain dynamics over time such a system will also likely require periodic retraining. In this context, open and reprogrammable analysis systems based on e.g. field programmable generic arrays (FPGA) or cellular neuronal networks (CNN, [24,29]) appear to be a promising venture.

ACKNOWLEDGMENT

I gratefully acknowledge contributions of R.G. Andrzejak, J. Arnhold, W. Burr, P. David, C. E. Elger, P. Grassberger, T. Kreuz, F. Mormann, and C. Rieke. This work was supported by the Deutsche Forschungsgemeinschaft.

REFERENCES

- [1] S.S. Viglione, G.O. Walsh, "Epileptic seizure prediction", *Electroencephalogr. clin. Neurophysiol.*, vol. 39, pp. 435-436, 1975.
- [2] Z. Rogowski, I. Gath, E. Bental, "On the prediction of epileptic seizures", *Biol. Cybern.*, vol. 42, pp. 9-15, 1981.
- [3] J. Gotman, J. Ives, P. Gloor, A. Olivier, L.F. Quesney, "Changes in inter-ictal EEG spiking and seizure occurrence in humans", *Epilepsia*, vol. 23, pp. 432-433, 1982.
- [4] H.H. Lange, J.P. Lieb, J. Jr. Engel, P.H. Crandall, "Temporo-spatial patterns of pre-ictal spike activity in human temporal lobe epilepsy", *Electroencephalogr. clin. Neurophysiol.*, vol. 56, pp. 543-555, 1983.
- [5] A. Katz, D.A. Marks, G. McCarthy, S.S. Spencer, "Does interictal spiking rate change prior to seizures?" *Electroencephalogr. clin. Neurophysiol.*, vol. 79, pp. 153-156, 1991.
- [6] R.B. Duckrow, S.S. Spencer, "Regional coherence and the transfer of ictal activity during seizure onset in the medial

- temporal lobe", *Electroencephalogr. clin. Neurophysiol.*, vol. 82, pp. 415-422, 1992.
- [7] B. Litt et al., "Epileptic seizures may begin hours in advance to clinical onset: a report of five patients. *Neuron*, vol. 30, pp. 51-64, 2001.
- [8] F. Mormann, K. Lehnertz, P. David, C.E. Elger, "Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients", *Physica D*, vol. 144, pp. 358-369, 1999.
- [9] I. Osorio, M.G. Frei, S.B. Wilkinson, "Real-time automated detection and quantitative analysis of seizures and short-term prediction of clinical onset", *Epilepsia*, vol. 39, pp. 615-627, 1998.
- [10] Y. Salant, I. Gath, O. Henriksen, "Prediction of epileptic seizures from two-channel EEG", *Med. Biol. Eng. Comput.*, vol. 36, pp. 549-556, 1998.
- [11] H. Kantz, T. Schreiber, *Nonlinear time series analysis*. Cambridge UK: Cambridge University Press, 1997.
- [12] J. Arnhold, P. Grassberger, K. Lehnertz, C.E. Elger, "A robust method for detecting interdependencies: application to intracranially recorded EEG", *Physica D*, vol. 134, pp. 419-430, 1999.
- [13] C.E. Elger, K. Lehnertz, "Prediction of epileptic seizures in humans from nonlinear dynamics analysis of brain electrical activity", *Eur. J. Neurosci.*, vol. 10, pp. 786-789, 1998.
- [14] L.D. Iasemidis, J.C. Sackellares, H.P. Zaveri, W.J. Williams, "Phase space topography and the Lyapunov exponent of electrocorticograms in partial seizures", *Brain Topogr.*, vol. 2, pp. 187-201, 1990.
- [15] L.D. Iasemidis, J.C. Principe, J.M. Czaplewski, R.L. Gilmore, S.N. Roper, J.C. Sackellares, "Spatiotemporal transition to epileptic seizures: a nonlinear dynamical analysis of scalp and intracranial EEG recordings" In: *Spatiotemporal Models in Biological and Artificial Systems* F.H. Lopes da Silva, J.C. Principe, L.B. Almeida, Eds., Amsterdam; IOS Press, 1997, pp. 81-88.
- [16] M. Le Van Quyen, J. Martinerie, M. Baulac, F. Varela, "Anticipating epileptic seizures in real time by a non-linear analysis of similarity between EEG recordings", *Neuroreport*, vol. 10, pp. 2149-2155, 1999.
- [17] M. Le Van Quyen, C. Adam, J. Martinerie, M. Baulac, S. Clemenceau, F. Varela, "Spatio-temporal characterizations of non-linear changes in intracranial activities prior to human temporal lobe seizures", *Eur. J. Neurosci.*, vol. 12, pp. 2124-2134, 2000.
- [18] M. Le Van Quyen et al., "Anticipation of epileptic seizures from standard EEG recordings", *Lancet*, vol. 357, pp. 183-188, 2001.
- [19] K. Lehnertz, C.E. Elger, "Can epileptic seizures be predicted? Evidence from nonlinear time series analyses of brain electrical activity", *Phys. Rev. Lett.*, vol. 80, pp. 5019-5023, 1998.
- [20] J. Martinerie et al., "Epileptic seizures can be anticipated by non-linear analysis", *Nat. Med.*, vol. 4, pp. 1173-1176, 1998.
- [21] H.R. Moser, B. Weber, H.G. Wieser, P.F. Meier, "Electroencephalograms in epilepsy: analysis and seizure prediction within the framework of Lyapunov theory", *Physica D*, vol. 130, pp. 291-305, 1999.
- [22] N. Thomasson, T.J. Hoeppner, C.L. Webber, J.P. Zbilut, "Recurrence quantification in epileptic EEGs", *Phys. Lett. A*, vol. 279, pp. 91-101, 2001.
- [23] A. Petrosian, D. Prokhorov, R. Homan, R. Dasheiff, D. Wunsch, "Recurrent neural network based prediction of epileptic seizures in intra- and extracranial EEG", *Neurocomputing*, vol. 30, pp. 201-218, 2000.
- [24] R. Tetzlaff, R. Kunz, C. Ames, D. Wolf, "Analysis of brain electrical activity in epilepsy with Cellular Neural Networks", *IEEE Proc. Eur. Conf. Circuit Theory Design*, pp. 573-577, 1999.
- [25] A.B. Geva, D.H. Kerem, "Forecasting generalized epileptic seizures from the EEG signal by wavelet analysis and dynamic unsupervised fuzzy clustering", *IEEE Trans. Biomed. Eng.*, vol. 45, pp. 1205-1216, 1998.
- [26] K. Lehnertz, C. E. Elger, "Spatio-temporal dynamics of the primary epileptogenic area in temporal lobe epilepsy characterized by neuronal complexity loss", *Electroencephalogr. clin. Neurophysiol.*, vol. 95, pp. 108-117, 1995.
- [27] R.G. Andrzejak, G. Widman, K. Lehnertz, C. Rieke, P. David, C.E. Elger, "The epileptic process as nonlinear deterministic dynamics in a stochastic environment – an evaluation of mesial temporal lobe epilepsy", *Epilepsy Res.*, vol. 44, pp. 129-140, 2001.
- [28] L.D. Iasemidis, P. Sardalos, J.C. Sackellares, D.S. Shiau, "Quadratic binary programming and dynamical system approach to determine the predictability of epileptic seizures", *J. Comb. Optim.*, vol. 5, pp. 9-26, 2001.
- [30] L.O. Chua, *CNN: A Paradigm for complexity*. Singapore: World Scientific Series on Nonlinear Science, 1998.